The future: treating specific endotypes

Prof. Peter J. Barnes
Head of Respiratory Medicine
Airway Disease
National Heart & Lung Institute
Dovehouse St
SW3 6LY London
UNITED KINGDOM
p.j.barnes@imperial.ac.uk

AIMS

- To distinguish between endotypes, phenotypes and clinical syndromes
- To consider examples of endotypes in asthma: aspirin-sensitive asthma, eosinophilic asthma, neutrophilic asthma, paucigranulocytic asthma
- To consider endotypes in asthma: alpha1-antitrypsin deficiency, telomerase defect, frequent exacerbator? chronic bronchitis vs emphysema?
- To discuss how identifying specific pathobiological mechanisms may influence development of new therapies

SUMMARY

Clinicians recognise disease syndromes from a collection of clinical features and diagnostic tests, but syndromes such as asthma and COPD clearly contain several different specific diseases. These might be discriminated by different phenotypes, which are the observable characteristics that occur together to define a phenotype. It is hoped that identifying phenotypes by cluster analysis might discriminate patients that will respond better to therapy. The problem has been that the clusters identified can often not be reproduced across different study populations and may not be stable over time. Endotypes refer to a distinct subgroup of a disease that has a specific pathobiological mechanism. The logical treatment for endotypes is to use a selective treatment that targets that particular mechanism as a more precise therapy that may have a better outcome in terms of treating disease but may also have less adverse effects.

Unfortunately there are very few examples within asthma and COPD where specific disease mechanisms have been identified and particularly mechanisms that lead to a different treatment approach.

Amongst asthmatic patients the majority have underlying atopy that leads to allergic inflammation in the airways. These patients have positive skin-prick test to common allergens that may suggest that specific immunotherapy (SIT) or complete allergen avoidance may be the most specifically targeted therapy. However SIT has usually been found to be ineffective in the treatment of asthma, suggesting that other allergens and other mechanisms are involved. Allergen avoidance is also usually ineffective, except for the case of early removal from occupational sensitisers. Non-atopic asthma, where there is no evidence of allergy measured by skin test or specific IgE, has a very similar pathology to allergic asthma and indeed there may be local IgE production, but the treatment of non-allergic (intrinsic) asthma is currently identical to extrinsic asthma, given the inefficacy of SIT. Aspirin-sensitive asthma appears to be a specific endotypes with a distinct clinical presentation (usually preceded by rhinitis and nasal polyps). It appears to be due to decreased prostaglandins and increased cysteinyl-leukotriene production and may be due to genetic polymorphisms of LTC4 synthase [1]. The logical treatment is therefore anti-leukotriene therapy, with a cys-LT1-receptor antagonist or a 5'-lipooxygenase inhibitor. In fact there treatments are not particularly effective and inhaled corticosteroids seems to be more effective in these patients [2].
Different inflammatory phenotypes are seen in asthma based on the pattern of sputum inflammation [3]. The majority of asthmatic patients have increased eosinophils in sputum and it is known that this pattern of inflammation is driven by Th2 cells or, in the case of intrinsic asthma, ILC2 cells through the activation of the transcription factor GATA3. Specific antibodies that target T2 cytokines, such as IL-5 and IL-4/13 have now been developed and may be indicated for particular patients with this pattern of asthma [4]. What is not clear is which patients would benefit most from anti-IL-5 or anti IL-4/13. But even these specific treatments may be insufficient alone, since blocking antibodies have little effect on lung function, symptoms or airway hyperresponsiveness. Another inflammatory pattern in neutrophilic predominance and these patients tend to be less responsive to corticosteroids but may benefit from a more anti-neutrophilic therapy. So far anti-IL-17, which targets neutrophilic inflammation has not been effective in asthma [5]. Macrolides appear to benefit some patients with neutrophilic asthma, either through their antibacterial effect or through their anti-inflammatory effect that targets NF-κB [6].

While there are clearly different clinical phenotypes of COPD, this has little influence on treatment so far. Some patients with COPD have predominant small airway disease, whereas others have predominant emphysema. While the SAD patients benefit more from bronchodilators, there is also some benefit in emphysema patients so this is not important in deciding therapy. Frequent exacerbators may differ from infrequent exacerbators and may benefit more from inhaled corticosteroids or roflumilast, which targets neutrophilic inflammation. Alpha1-antitrypsin deficiency is a genetic form of COPD that presents early (in smokers) with panacinar emphysema [7]. These patients should theoretically derive most benefit form alpha-1 antitrypsin augmentation therapy, but in practice it is very expensive and difficult to maintain normal plasma levels. Another genetic cause of emphysema recently recognised is polymorphism of telomerase gene that determines telomere length [8]. These patients are usually female and present with early onset COPD. There is often a family history of idiopathic pulmonary fibrosis, where telomerase polymorphisms are commonly seen. Unfortunately there is no specific therapy available for this endotypes.

Asthma and COPD are distinct syndromes, but sometimes there is an overlap of features. Although this has been called asthma-COPD overlap syndrome (ACOS), it includes asthmatics with features of COPD (such as neutrophilic inflammation, fixed obstruction) and COPD patients with features of asthma (increased eosinophils, increased reversibility, greater response to corticosteroids) [9, 10]. This may represent the coincidence of two common diseases, but may also be a distinct phenotype. Whether blood eosinophils are useful in predicting those COPD patients that respond to corticosteroid is not yet certain [11, 12], but it is important to identify treatable traits, such as corticosteroid responsiveness in COPD patients and restrict the use of ICS in COPD to these patients.

Far more research is needed to identify endotypes that may be targeted with precision medicines, but even after identifying a specific endotype there may be no specific therapy that targets the specific abnormality.

REFERENCES


